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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/580,709 | 05/25/2006 | Paul Vermeij | I-2003.023 US | 1731 |

31846 7590 07/08/2009

Intervet/Schering-Plough Animal Health
Attn: Jill Corcoran
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| EXAMINER | |
|---|---|
| FORD, VANESSA L | |
| ART UNIT | PAPER NUMBER |
| 1645 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 07/08/2009 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/580,709 | VERMEIJ, PAUL | |
| | Examiner | Art Unit | |
| | VANESSA L. FORD | 1645 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *31 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-5 and 17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 May 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. This action is responsive to Applicant's amendment and response filed March 31, 2009. Claims 1 and 5 have been amended. Claims 6-16 and 18-19 have been canceled. Claims 1-5 and 17 are under examination. A Non-Final action is set forth below.

### *Rejections Withdrawn*

2. In view of Applicant's amendment and remarks the following rejections are withdrawn:

(a) objection to the specification, pages 2-3, paragraph 2.

(b) objection to the specification, page 3, paragraph 3.

(c) objection to the specification, page 3, paragraph 4.

(d) objection to the specification, page 4, paragraph 5.

(e) objection to the specification, page 4, paragraph 5.

(f) objection of claim 1, page 4, paragraph 6.

(g) rejection claims 1-5 and 17 under 35.U.S.C. 101, page 4, paragraph 7.

(h) rejection of claims 1-5, 9-12 and 17 under 112 first paragraph, pages 4-9, paragraph 8.

(i) rejection of claims 1-5, 9-12 and 17 under 112 first paragraph, pages 9-12, paragraph 9.

(j) rejection of claims 1-5, 9-12 and 17 under 112 first paragraph, pages 16-20, paragraph 11.

(k) rejection of claims 1-5, 9-12 and 17 under 102(b), pages 20-22, paragraph 12.

(l) rejection of claims 1-2 under 102(b), pages 20-22, paragraph 13.

***Rejection Maintained***

***Enablement Regarding Host Cell***

3. Claim 4 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 4 is drawn to a live recombinant carrier comprising a nucleic acid according claim 1.

Applicants broadly claim a transgenic cell containing a host cell transfected or transduced with a recombinant vector that directs expression of a nucleic acid molecule as recited in claim 1. These claims read on a cell within a transgenic animal or human carrier. The breadth of the claim reads on the implementation of the transgenic cell in both *in vitro* and *in vivo* assays.

The state of the art at the time of filing was such that one of skill could not predict the phenotype of transgenics. For example, Overbeek *("Factors affecting transgenic animal production," Transgenic Animal Technology, 1994, pages 96-98)* taught that within one litter of transgenic mice, considerable variation in the level of transgene expression occurs between founder animals and causes different phenotypes (page 96, last paragraph). Wall (*Theriogenology, 1996,Vol. 45, pp. 57-68)* teaches that the art of

transgenic animals has for many years stated that the unpredictability lies, in part, with the site or sites of transgene integration into the target genome and that "the position effect" as well as unidentified control elements are recognized to cause aberrant expression of a transgene. The elements of the particular construct used to make transgenic animals are also held to be critical, and they must be designed case by case without general rules to obtain good expression of a transgene; e.g., specific promoters, presence or absence of introns, etc., see Houdebine, *(J. Biotech. Vol. 34, 1994, pages 269-287, specifically page 281).* Furthermore, transgenic animals are regarded to have within their cells, cellular mechanisms that prevent expression of the transgene, such as methylation or deletion from the genome, see Kappel, (*Current Opinions in Biotechnology, Vol. 3, 1992, pp. 548-553).*

Well-regulated transgene expression is not frequently achieved because of poor levels or the complete absence of expression or leaky expression in non-target tissues. See Cameron, *(Molec. Biol. 7, 1997, pages 253-265, specifically page 256, col. 1 -2, bridg. parag.).* Factors influencing low expression, or the lack thereof, are not affected by copy number and such effects are seen in lines of transgenic mice made with the same construct. See Cameron, *(Molec. Biol. 7, 1997, page 256, lines 3-9).* With regard to the importance of promoter selection, Niemann, *(Transg. Res. 7, 1997, pages 73-75)*,states "that transgenic pigs made with different promoters regulating expression of a growth hormone gene give disparate phenotypes - one deleterious to the pig, the other compatible with pig health" (pages 73-75, specifically page 73, col. 2, parag. 2, line 12 to page 73, col. 1, line 4).

Examples in the literature aptly demonstrate that even closely related species carrying the same transgene construct can exhibit widely varying phenotypes. Mullins, *(Hypertension, Vol. 22, 1993, pp. 630-633)* states that not all animals express a transgene sufficiently to provide a model for a disease as the integration of a transgene into different species of animal has been reported to give divergent phenotypes. For example, several animal models for human diseases have relied on transgenic rats when the development of mouse models was not feasible. Mullins (*Nature, Vol. 344, 1990, 541-544)* produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse *Ren-2* renin transgene. Hammer *(Cell, Vol. 63, 1990, 1099-1112)* describes spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human $_2$-microglobulin transgenes. Both investigations were preceded by the failure to develop human disease-like symptoms in transgenic mice expressing the same transgenes that successfully caused the desired symptoms in transgenic rats. See Mullins *(EMBO J., vol. 8, 1989, pages 4065-4072; Taurog et al, Jour. Immunol., Vol. 141, 1988, pages 4020-4023).* Mullins *(J. Clin. Invest. Vol. 98, 1996. pages S37-S40)* disclose that the use of non-murine species for transgenesis will continue to reflect the suitability of a particular species for the specific questions being addressed, bearing in mind that a given construct may react very differently from one species to another. Thus, at the time of filing, the phenotype of a transgenic cell contained within any animal was unpredictable and could not be prepared for any species.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect predicting the phenotype of transgenics or human carrier, 3) the reference cited above convey the state of the art regarding unpredictability of determining the phenotypes of trangenics or human carrier and 4) no working examples present in the specification regarding predicting the phenotypes of transgenic or human carrier, 6) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). One of skill in the art could not predict the phenotype of transgenics because of the lack of guidance in the art and in the instant specification in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation is undue.

In view of all of the above, in view of the lack of predictability in the art, it is determined that it would require undue experimentation to make and use the claimed invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-5 and 17 are rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites "encoding the 26 KD *Lawsonia intracellularis* protein of SEQ ID NO:2". It is unclear as to whether claim 1 used open or closed language? Does the isolated or purified nucleic acid of claim 1 encoding the *Lawsonia intracellularis* protein that "consists of SEQ ID NO.2" or Does the isolated or purified nucleic acid of claim 1 encoding the *Lawsonia intracellularis* protein that "comprises SEQ ID NO.2"? Clarification/correction is required.

5. Claim 2 is rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 2 recites " a DNA fragment comprising a nucleic acid according to claim 1". A DNA fragment cannot comprise the nucleic acid molecule encoding the 26 kD *Lawsonia intracellularis* protein as indicated in claim 2. It should be noted that a DNA fragment is less than the whole. Thus, the DNA fragment cannot be longer than the nucleic acid molecule that encodes the 26 kD *Lawsonia intracellularis* protein. Clarification/ correction is required.

### *Status of Claims*

6. No claims allowed.

### *Conclusion*

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to VANESSA L. FORD whose telephone number is (571)272-0857. The examiner can normally be reached on 9 am- 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on (571) 272-0756. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Vanessa L. Ford/
Examiner, Art Unit 1645
June 29, 2009